REMARKS

Applicant requests reconsideration. Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 were previously pending and are still pending and under examination in this application.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohlfing C. L., et al. (2000) and Chapin B. L., et al. (1999). According to the Examiner, Rodriguez-Moran teaches that elevated serum CRP levels have been found in type II diabetics and in diabetics with foot ulcers and that elevated serum CRP levels are also found in noncontrolled type II diabetic patients. The Examiner admits that "Rodriguez-Moran does not teach the characterizing [of] a risk profile for developing diabetes in an apparently healthy individual nor evaluating the likelihood that an individual will benefit from treatment."

The Examiner asserts that Rohlfing "teaches the use of a screening assay for undiagnosed diabetes and/or complications thereof (see particularly page 187 and CONCLUSIONS)." The Examiner also asserts that Chapin "teaches that even apparently healthy individuals who undergo regular physical examination can suffer from undiagnosed diabetes and/or complications thereof (see particularly Table 2)." According to the Examiner, "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type II diabetes, as taught by Rodriguez-Moran et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes as taught by Rohlfing et al., even in apparently healthy individuals because even apparently healthy individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al."

Applicant respectfully traverses the rejection. The instant claims are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations. The invention *predicts* the risk of a *future* disorder (diabetes or diabetic complication) *prospectively* (i.e.,

before the diabetic disorder happens) among *apparently healthy* individuals (i.e., individuals without current clinical evidence of disease) based on a level of C-reactive protein (CRP).

The Examiner admits that Rodriguez-Moran does not teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment."

Applicant submits that Rodriguez-Moran does not and could not address whether the level of CRP is *predictive* of a *future* diabetes or diabetic complications in *apparently healthy* individuals. Rodriguez-Moran did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Rodriguez-Moran compared the serum levels of CRP in patients with type II diabetes (i.e., after the diabetic disorder happened). Rodriguez-Moran found that patients with type II diabetes have higher levels of CRP compared to healthy controls. Patients with type II diabetes are <u>not</u> apparently healthy and data from such a group cannot be used to make conclusions regarding apparently healthy individuals.

Furthermore, the Rodriguez-Moran study only shows that patients with type II diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the study of Rodriguez-Moran one of ordinary skill in the art would have known that it is impossible to distinguish whether the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes because the CRP levels were measured after the diabetic disorder happened. In fact, the teachings of Rodriguez-Moran suggest that elevated CRP (a known marker of inflammation) might probably be the result of the diabetic condition rather than the cause of the diabetes (see Rodriguez-Moran et al. p. 215 right-hand column):

> "A probable involved pathway could be related to the raising of serum viscosity and shear stress associated to hyperglycemia, producing endothelium dysfunction and inflammation and in this way, increasing citokines release and thus elevating CRP levels."

Thus, Rodriguez-Moran does not address whether the level of CRP is *predictive* of *future* diabetes in individuals because if the elevation in the levels of CRP is the result of or is caused by the diabetes, the elevated levels of CRP cannot predict future diabetes (i.e., cannot predict diabetes before it happens). Therefore, the teachings of Rodriguez-Moran do not provide a reason for one of ordinary skill in the art to consider using levels of CRP to predict future diabetes.

The additional teachings of Rohlfing and Chapin do not cure the deficiency of the primary reference of Rodriguez-Moran. Rodriguez-Moran in combination with Rohlfing and Chapin does not teach or suggest all the limitations of instant claims.

The Examiner alleges that Chapin "teaches that even apparently healthy individuals who undergo regular physical examination can suffer from undiagnosed diabetes and/or complications thereof (see particularly Table 2)." Applicant disagrees with the Examiner's characterization of the teachings of Chapin that they are directed to *apparently healthy* individuals. The subjects of Chapin are described as *asymptomatic*. The subjects in Chapin with asymptomatic diabetes are not apparently healthy as defined in the instant application. Apparently healthy individuals, as defined in the specification on page 9, lines 4-7, are individuals who have not had any clinical evidence of diabetes and who do not otherwise exhibit symptoms of disease. When the asymptomatic subjects in Chapin were tested they were found to have clinical evidence of diabetes. The three subjects in Chapin who were characterized as having asymptomatic diabetes were identified as having diabetes because, upon blood glucose testing, they satisfied both the WHO criterion of 2-h glucose concentration $\geq$ 11.1 mmol/l (200 mg/dl) and the ADA criterion of fasting glucose concentration $\geq$ 6.99 mmol/l (126 mg/dl) (See Chapin page 428, middle column). Thus, the subjects with asymptomatic diabetes in Chapin have clinical evidence of diabetes and would not be classified as apparently healthy.

In view of the above, the combination of Rodriguez-Moran and Rohlfing and Chapin does not teach or suggest all the limitations of instant claims. Accordingly, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as unpatentable over Rodriguez-Moran in view of Rohlfing and Chapin is respectfully requested.

The Examiner rejected claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohlfing C. L., et al. (2000) and Chapin B. L., et al. (1999). The Examiner asserts that Schalkwijk teaches that elevated serum CRP levels have been found in type I diabetes and in diabetics with foot ulcers particularly referring to the Results on page 211 and to Table 2. The Examiner admits that Schalkwijk that does not teach

characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment."

The Examiner alleges that, "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type I diabetes, as taught by Schalkwijk et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes as taught by Rohlfing et al., even in apparently healthy individuals because even apparently healthy individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al."

Applicant respectfully traverses the rejection. Similar arguments to those presented above in response to the rejection of the claims as obvious in view Rodriguez-Moran are applicable here. As stated above, the instant claims all are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations.

Schalkwijk does not, and could not, address whether a level of CRP is predictive of developing diabetes or diabetic complications or whether an apparently healthy individual (i.e., without diabetes) would benefit from prophylactic treatment to prevent diabetes or diabetic complications. Schalkwijk did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Schalkwijk compared the serum levels of CRP in type I diabetic patients (i.e., after the diabetic disorder happened). Schalkwijk teaches that patients with type I diabetes had higher serum levels of CRP. It should be noted that the study of Schalkwijk was not designed in a manner that would permit one to conclude that elevated levels of CRP predict diabetes. The Schalkwijk study only shows that patients with diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the data in Schalkwijk, one of ordinary skill in the art would have known that it is impossible to conclude definitively that the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes because the CRP levels were measured after the diabetic disorder happened. In fact, the teachings of Schalkwijk suggest that elevated CRP is more likely the result of the diabetic condition rather than the cause of the diabetes (see Schalkwijk p. 356):

> "Various possible mechanisms could induce chronic low degree inflammation in diabetes, including activation of macrophages, increased oxidative stress or an induction of cytokines. One of the pathophysiological consequences of hyperglycaemia is the phenomenon of nonenzymatic glycation and the formation of advanced glycation end products (AGEs). AGEs have been shown to activate macrophages, to increase oxidative stress and to induce, in macrophages, the synthesis of interleukin-1 and tumor necrosis factor-α and, in vivo in mice, the expression of interleukin-6 mRNA. Many of the possible mechanisms leading to chronic low degree inflammation could be related to nonenzymatic glycation. Another possibility is that increases in CRP are related to adipose-tissue-derived cytokines." (Citations omitted)

Thus, Schalkwijk does not address whether the level of CRP is *predictive* of diabetes in *apparently healthy* individuals because if the elevation in the levels of CRP is the result of or is caused by the diabetes, the elevated levels of CRP cannot predict future diabetes (i.e., cannot predict diabetes before it happens). Therefore, the teachings of Schalkwijk do not provide a reason for one of ordinary skill in the art to consider using levels of CRP to predict future diabetes.

The additional teachings of Rohlfing and Chapin do not cure the deficiency of the primary reference of Schalkwijk. Schalkwijk in combination with Rohlfing and Chapin does not teach or suggest all the limitations of instant claims. The arguments presented above by the Applicant in reference to the teachings of Chapin are reiterated and are applicable here.

In view of the above, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as unpatentable over Schalkwijk in view of Rohlfing and Chapin is respectfully requested

In the paragraph bridging pages 3 and 4 of the Office Action, the Examiner asserts that the "Applicant makes a curious argument that the teachings of Rodriguez-Moran et al. cannot be used to render obvious the predictive value of CRP levels for future diabetes. Applicant is advised that if this argument were to be found persuasive, then a rejection for lack of enablement would be required given the fact that the example in the specification does not show said predictive value either." The Examiner alleges that "the subjects of the study were merely *asked* if they were free of diabetes; there is no showing that they were free from uncontrolled diabetes at the time of their enrollment in the study (page 24)."

Applicant respectfully disagrees with the Examiner's assertions. The subjects of the study described in the specification were WHS (Women's Health Study) participants who provided blood specimens and were free of reported diabetes at enrollment and subsequently developed newly diagnosed diabetes during a four-year observation period. As stated in the Example, based on revised ADA diagnostic criteria, the cases were confirmed if one or more of the following conditions were met: (1) presence of > 1 classic symptom of hyperglycemia (polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision) plus either a fasting glucose > 126 mg/dl ([7.0 mmol/l]) or random plasma glucose > 200 mg/dl ([11.1 mmol/l]), or (2) in the absence of symptoms, > 2 elevated plasma glucose concentrations (fasting > 126 mg/dl ([7.0 mmol/l]), random > 200mg/dl ([11.1 mmol/l]), or 2-hour plasma glucose > 200mg/dl ([11.1 mmol/l]) during oral glucose tolerance testing), or (3) use of insulin or oral hypoglycemic agent. In addition, in order to reduce misclassification bias due to undiagnosed diabetes at study entry, individuals diagnosed within the first year of follow-up (n=69) were excluded from the study (See pages 24-25 of the specification).

Furthermore, due to the high prevalence of undiagnosed diabetes among middle-aged Americans and because the study was designed to evaluate the role of inflammation as a determinant of future diabetes, the sample was limited to individuals with baseline hemoglobin A1c < 6.5%, a reference value commonly used in clinical practice. Participants with missing values for baseline clinical covariates of interest were also eliminated from the analysis (body-mass index, 3% of cases and 1.5% of controls; history of hypertension 0.5% of cases and 0.7% of controls; history of hyperlipidemia, 0.5% of controls; and use of hormone replacement therapy, 0.3% of controls) (See page 25 of the specification).

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Ridker et al., Applicant

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Docket No.: B0801.70238US00
Date: May 6, 2008
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